

Physical interventions to interrupt or reduce the spread of respiratory viruses.

Part 1 - Face masks, eye protection and person distancing: systematic review and meta-analysis

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Abstract

OBJECTIVE: To examine the effectiveness of eye protection, face masks, or person distancing on interrupting or reducing the spread of respiratory viruses.

DESIGN: Update of a Cochrane review that included a meta-analysis of observational studies during the SARS outbreak of 2003.

DATA SOURCES: Eligible trials from the previous review; search of Cochrane Central Register of Controlled Trials, PubMed, Embase and CINAHL from October 2010 up to 1 April 2020; and forward and backward citation analysis.

DATA SELECTION: Randomised and cluster-randomised trials of people of any age, testing the use of eye protection, face masks, or person distancing against standard practice, or a similar physical barrier. Outcomes included any acute respiratory illness and its related consequences.

DATA EXTRACTION AND ANALYSIS: Six authors independently assessed risk of bias using the Cochrane tool and extracted data. We used a generalised inverse variance method for pooling using a random-effects model and reported results with risk ratios and 95% Confidence Intervals (CI).

RESULTS: We included 15 randomised trials investigating the effect of masks (14 trials) in healthcare workers and the general population and of quarantine (1 trial). We found no trials testing eye protection. Compared to no masks there was no reduction of influenza-like illness (ILI) cases (Risk

Ratio 0.93, 95%CI 0.83 to 1.05) or influenza (Risk Ratio 0.84, 95%CI 0.61-1.17) for masks in the general population, nor in healthcare workers (Risk Ratio 0.37, 95%CI 0.05 to 2.50). There was no difference between surgical masks and N95 respirators: for ILI (Risk Ratio 0.83, 95%CI 0.63 to 1.08), for influenza (Risk Ratio 1.02, 95%CI 0.73 to 1.43). Harms were poorly reported and limited to discomfort with lower compliance. The only trial testing quarantining workers with household ILI contacts found a reduction in ILI cases, but increased risk of quarantined workers contracting influenza. All trials were conducted during seasonal ILI activity.

CONCLUSIONS: Most included trials had poor design, reporting and sparse events. There was insufficient evidence to provide a recommendation on the use of facial barriers without other measures. We found insufficient evidence for a difference between surgical masks and N95 respirators and limited evidence to support effectiveness of quarantine. Based on observational evidence from the previous SARS epidemic included in the previous version of our Cochrane review we recommend the use of masks combined with other measures.

Introduction

Epidemic and pandemic respiratory infections pose a serious threat to people worldwide. Recent pandemics were the H1N1 influenza caused by the H1N1pdm09 virus in 2009 and the current Coronavirus Disease-2019 - COVID-19 - caused by SARS-CoV-2; recent epidemics of note were the Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS), which began in 2012. Even non-epidemic acute respiratory infections (ARIs) place a huge burden on the healthcare systems of countries and are a prominent cause of morbidity.¹ In addition, ARIs are often pre-cursors to lower respiratory tract infections (e.g. pneumonia) caused by bacterial pathogens which cause millions of deaths worldwide.

Epidemics and pandemics are more likely following antigenic change in the virus or transmission from animals (domestic or wild) when there is no natural human immunity.² High viral load, high levels of transmissibility, susceptible populations and symptomatic patients are considered to be the drivers of such epidemics and pandemics.³ Most single intervention measures (such as the use of vaccines or antivirals) will be insufficient to contain the spread of influenza⁴⁵; but combinations of measures may reduce the reproduction number below 1. For some infectious agents, there are no licensed interventions. Stopping the spread of the virus from person to person via a combination of social and physical interventions may be the only option to reduce the spread of outbreaks.

Physical interventions, such as the use of masks and person distancing measures, might prevent the spread of virus transmitted by aerosols or large droplets from infected to susceptible people. Use of hand hygiene, gloves, and protective gowns can also prevent the spread by limiting the transfer of viral particles onto and from surfaces. Such interventions were emphasized in WHO's latest Global Influenza Strategy 2019 – 2030⁶ and can have several possible advantages over other methods of suppressing ARI outbreaks: they can be instituted rapidly and may be independent of any specific type of infective agent including novel viruses.

The benefits of physical interventions are self-evident and have been confirmed by evidence included in three previous reviews.⁷⁸ Given the global importance of interrupting viral transmission in the current COVID-19 pandemic, up-to-date estimates of their effectiveness are necessary to inform planning, decision-making, and policy. In this review we concentrate on the evidence for use of eye protection or masks and the effects of person distancing. The next part of this review will include evidence for all other physical interventions.

Methods

Inclusion criteria

We included randomised controlled trials (RCT) and cluster-randomised controlled trials (C-RCT) including people of any age that tested the use of face masks (i.e. surgical or medical masks and N95 respirators), eye protection, or person distancing against standard practice, or a similar physical barrier, or compared any of these interventions. We only included studies that reported a measure of acute respiratory illness – such as influenza-like illness, influenza, or respiratory infections – and/or its consequences (e.g. days off work, complications, hospitalisation and death, if clearly reported as consequences of the respiratory illness). We also included relevant studies from the previous versions of this review.⁷⁻⁹

Search strategy

We identified RCTs and C-RCTs studying effectiveness of eye protection (any purposed device excluding simple eyeglasses), masks (defined as any type of facial mask), and person distancing from our 2011 review.⁸ These earlier studies were analysed using word frequency to create a new search string that was run in PubMed.¹⁰ This search string was converted using the Polyglot Search Translator¹¹ and run in the following additional databases; the Cochrane Central Register of Controlled Trials, Embase and CINAHL. The search covered the dates October 2010 to 9 March 2020. Search strings for all databases are available in the appendices (Appendix 1). A backwards and forward citation analysis, using Scopus, was conducted on all new studies retrieved. Search and citation analysis results were screened using the RobotSearch tool to remove all obvious non-RCTs.¹² Three authors (JC, MJ and ST) independently reviewed the titles and abstracts of the identified studies to assess eligibility for inclusion. Discrepancies were resolved by consensus.

Risk of bias assessment

Risk of bias was assessed by three author pairs independently (TJ, EB, LA, GB, MJ, EF) for the method of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), outcome reporting (attrition bias), and selective reporting (reporting bias). We used the Cochrane risk of bias

tool.¹³ For each item risk was either 'high', 'low' or 'unclear'. Low risk of bias for the method of random sequence generation indicates that the method was well-described and is likely to produce balanced and truly random groups; for allocation concealment that the next treatment allocation was not known to participant/cluster or treating staff until after consent to join the study; for blinding of participants and personnel that the method is likely to maintain blinding throughout the study; for blinding of outcome assessors that all assessing outcomes were unaware of treatment allocation; for outcome reporting that participant attrition through the study is reported and reasons for loss are appropriately described; and for selective reporting that all likely planned and collected outcomes have been reported.

Data extraction and analysis

Six authors (TJ, EB, LA, GB, MJ, EF) independently extracted data in pairs. Discrepancies were resolved by consensus. Descriptions of the interventions were extracted using the Template for Intervention Description and Replication (TIDieR) template.¹⁴ We entered outcome data in RevMan software and used a generalised inverse variance random effects method for pooling. The effect estimate was expressed as a risk ratio with 95% confidence interval. We calculated the I^2 statistic for each pooled estimate to assess statistical heterogeneity.¹⁵ For studies that could not be pooled we report the effect estimates as reported by the study authors. We conducted a subgroup analysis for interventions aimed at protecting health care workers.

Differences between 2009 review and current review

The 2009 review included both randomised trials, cluster randomised trials, and observational studies. This update excluded the latter. This update was also split into two parts, according to intervention categories. This Part 1 is focussed on face masks, eye protection, and person distancing; Part 2 will address all other categories of physical interventions.

Results

Results of the search

The updated search yielded 2468 references after removal of duplicates of which 2345 were excluded. A further 42 were excluded after review of the full text paper. Backwards and forward citation analysis identified a further 20 studies resulting in a total of 101 papers testing a range of barrier interventions aimed at interrupting the spread of respiratory viruses. For this part 1 of our review we included 15 RCT/c-RCTs, including 5 trials from the 2011 review¹⁶⁻²⁰ (see Figure 1).

Risk of bias

Reporting of sequence generation, allocation concealment (particularly in cluster-randomised trials) and blinding of outcome assessment was poor, leading to an unclear risk of bias judgement for 30% of studies (see Figure 2). The majority of studies were unblinded due to the nature of the masks, or insufficient information (70% of studies with high or unclear risk of bias). Only one study was blinded to staff.²¹ For the remainder of the unblinded studies at low risk of bias, this was due to them having objective outcomes that were unlikely to be affected by unblinding. More than 80% of studies had no evidence of serious attrition and described reasons for losses to follow-up well. 70% of studies had no evidence of selective outcome reporting. One study had what appeared to be selective testing or reporting of viral tests, another had selective reporting of non-viral isolates and changes during the study that made planned outcomes unclear. The remainder of the studies had unclear risk of bias for this domain due to insufficient information reported.

Eye protection

We found no trials on the use of eye protection as a single intervention.

Masks

Nine trials compared masks with no masks.^{16-18 21-26} Two of these studies included health care workers^{18 25} and 7 others included people living in the community. All trials were conducted in non-pandemic settings. A description of the interventions is presented in Table 1. Included trials are

described in Table 2. Pooling of all nine trials did not show a statistically significant reduction of ILI cases (Risk Ratio 0.93, 95%CI 0.83 to 1.05) or laboratory-confirmed influenza cases (Risk Ratio 0.84, 95%CI 0.61-1.17) in the group wearing a mask compared to those not wearing a mask (see Figure 3a). Eight-seven percent of the weight of this analysis is carried by two studies from the same first author.^{16 22} A separate analysis of the two trials in healthcare workers also failed to show a statistically significant difference between the mask and no mask groups (Risk Ratio 0.37, 95%CI 0.05 to 2.50).

Five trials compared surgical masks with N95/P2 respirators.^{25 27-30} All trials except MacIntyre 2009²⁰ included healthcare workers. Pooling of four trials showed no difference between surgical/medical face masks and N95 respirators for rates of clinical respiratory illness (Risk Ratio 0.70, 95%CI 0.45 to 1.10), for ILI (Risk Ratio 0.83, 95%CI 0.63 to 1.08), or for laboratory-confirmed influenza (Risk Ratio 1.02, 95%CI 0.73 to 1.43) (see Figure 3c). If only studies in healthcare workers are compared the Risk Ratio for ILI is 0.64, 95%CI 0.32 to 1.31. The outcomes 'clinical respiratory illness' and ILI were reported separately by the authors. Considering how these outcomes were defined it is highly likely that there is considerable overlap between the two and therefore these outcomes were not combined into a single clinical outcome. Harms were poorly reported, but generally discomfort wearing masks was mentioned²⁴ and Radonovich³⁰ mentioned that participants wearing the N95 respirator reported skin irritation and worsening of acne.

MacIntyre 2015²⁵ also included a trial arm with cloth masks and found that the rate of ILI was higher in the cloth mask arm compared to medical/surgical masks (RR 13.25, 95%CI 1.74 to 100.97) and compared to no masks (RR 3.49, 95%CI 1.00 to 12.17).

Person distancing

One trial evaluated the effectiveness of quarantining workers of one of two sibling companies in Japan whose family members developed an influenza-like illness (ILI) during the 2009-2010 H1N1 influenza pandemic.³¹ Workers in the intervention group were asked to stay home on full pay until 5

days after the household member(s) showed resolution of symptoms or 2 days after alleviation of fever. Compliance was 100%. In the intervention group 2.75% of workers contracted influenza, compared with 3.18% in the control group (Cox Hazard Ratio 0.799, 95%CI 0.658 to 0.970, p=0.023), indicating a 20% reduction of infection in the intervention group. However, the risk of a worker being infected was 2.17-fold higher in the intervention group where workers stayed at home with their infected family members. The authors conclude that quarantining workers with infected household members could be a useful additional measure to control spread of respiratory viruses in an epidemic setting.

Discussion

Main findings

Our results show that masks alone have no significant effect in interrupting spread of ILI RR 0.93 (95% CI 0.83 to 1.05) or influenza RR 0.84 (95% CI 0.61 to 1.17) in the all populations analysis. Our findings are similar for ILI in healthcare workers RR 0.37 (95% CIs 0.05 to 2.50) and for the comparisons between N95 respirators and surgical masks: RR 0.70 (95% CI 0.45 to 1.10) for clinical respiratory illness, RR 0.83 (95% CI 0.63 to 1.08) and influenza RR 1.02 (95% CI 0.73 to 1.43). Five of the trials contributing to the analysis were carried out by members of the same group.^{20 25 26 28 29} On the basis of one trial²⁵ cloth surgical masks should not be used as they are associated with a higher risk of ILI and penetration of microorganisms. In general, harms were not or poorly reported, with general discomfort resulting in reduced compliance with wearing being the main issues.

One trial testing person distancing found a reduction in transmission to co-workers when those with infected household members stay home from work. However, staying home increased their risk of being infected two-fold. We were disappointed to find only one trial on person distancing which is currently the core of the global containment strategy. This points to the difficulty and lack of interest in carrying out such studies.

Even though this update of the review focussed only on randomised and cluster randomised trials, the available body of evidence is inconclusive. We found a body of relatively small trials conducted mostly in a non-epidemic context (low viral circulation), with the exception of the largest study which crossed during the active study period two of the highest reporting years for influenza in the United States, between 2010-2017.³² The two largest studies with respect to event rates^{19 30} are consistent regarding the direction of their findings of no differences between surgical or N95 masks.

Collectively, the evidence base was of variable quality. Inadequate reporting of sequence generation and allocation concealment was common. While allocation concealment of cluster-randomised trials is important this was rarely reported. Due to the nature of the intervention comparison, most trials were unblinded. However, blinding of outcome assessment is highly feasible and highly desirable, but was rarely done or reported. Outcomes were poorly defined with lack of clarity as to possible etiology of the agents (bacterial vs viral) in some studies. The cluster trials had insufficient attention paid to adjusting sample size calculations and analysis for clustering. As a consequence many trials were underpowered and had spuriously narrow confidence intervals around the effect size. The variable quality of the studies places some limits on the generalisability to the current COVID-19 epidemic, albeit it is a respiratory virus with a similar mode of transmission to those in the reviewed studies.

Comparison with other reviews

In a meta-analysis comparing surgical masks with N95 respirators Smith³³ pooled three trials^{19 28 29} and found no significant difference (OR 0.89, 95% CI 0.64 to 1.24) for laboratory-confirmed respiratory infections or ILI (OR 0.51, 95% CI 0.19 to 1.41). A similar meta-analysis by Offeddu et al³⁴ concluded that based on two studies by MacIntyre et al^{25 28} masks (either surgical masks or N95 respirators) were effective against clinical respiratory infections (RR 0.59, 95% CI 0.46 to 0.77) and ILI

(RR 0.34, 95% CI 0.14 to 0.82). Pooling the same two studies they also found that N95 respirators were superior to surgical masks for Clinical respiratory infections (RR 0.47, 95% CI 0.36 to 0.62), but not for ILI (RR 0.59, 95%CI 0.27 to 1.28).³⁴ The most recent meta-analysis by Long et al³⁵ included 5 studies comparing surgical masks with N95 respirators and found no difference (RR 1.09, 95% CI 0.92 to 1.28) against neither influenza nor respiratory viral infections (RR 0.89, 95% CI 0.70 to 1.11).³⁵ By excluding the Loeb¹⁹ study (an open non-inferiority randomised, controlled trial carried out to compare the surgical mask with the N95 respirator in protecting healthcare workers against influenza) the authors found a significant effect against viral infections (RR 0.61, 95% CI 0.39 to 0.98). The authors do not report a rationale for the exclusion in the sensitivity analysis and do not report on exclusion of the studies with low weighting which arguably would be more relevant in a sensitivity analysis. The two studies which make up 96% of the weighting^{19 30} clearly demonstrate no difference in the outcome events.

The findings from several systematic reviews and meta-analyses over the last decade have not demonstrated any significant difference in the clinical effectiveness of N95 respirators or equivalent compared to the use of surgical masks when used by healthcare workers in multiple health care settings for the prevention of respiratory virus infections, including influenza.

Our 2011 review⁸ showed a clear protective effect of wearing surgical masks and hygienic measures compared to not wearing masks in the SARS 2003 outbreak (RR 0.32, 95% CIs 0.26 to 0.39). The evidence was based on case-control studies carried out during the outbreak.

Relevance of the Findings in the Clinical Setting

Our findings are highly relevant in the setting of epidemic and pandemic respiratory infections and the current global pandemic of COVID-19 underscores the point. The evidence supports that SARS-CoV-2 is spread through respiratory droplets and/or contact routes which places it in the route of

transmission for which health care workers would be required to wear masks.^{36 37} The WHO China Joint Mission on COVID-19 of 75,465 cases supports person-to-person droplet and fomite transmission, with the majority of transmission occurring within families in close contact with each other.³⁶ A recent report in a clinical setting of intubation and non-invasive ventilation in which 41 health care workers were exposed over a prolonged period a within close proximity to a COVID-19 + patient revealed no transmission events to the Health care workers based on repeated testing during which majority (85%) of the health care workers were wearing a surgical mask and other appropriate PPE while the remainder wore an N95 respirator. This latter finding supports the results of the studies which were reviewed and brings into focus the importance of the use of masks as a component of personal protective equipment in the current COVID-19 pandemic. The current COVID-19 pandemic has elicited conflicting recommendations with several institutions and countries suggesting that only N95 or equivalent masks should be used as a component of the personal protective equipment for health care workers and not a surgical mask. The WHO recommendations emphasize that in the setting of epidemic and pandemic respiratory virus infections transmitted predominantly by the droplet route, one of the most important elements is strict adherence in the use of personal protective equipment of which the facial mask is only one component³⁸ and suggest surgical masks for routine care and reserve the N95 mask for aerosol generating medical procedures. Despite the methodological issues outlined, our review of the available literature did not find any differences in the clinical effectiveness of either type of mask in the setting of respiratory viral infection transmission to health care workers. Our review also identified a dearth of reported findings related to the harms of N95 respirators and they need to be considered in any RCTs or C-RTs, especially in the setting of a global pandemic with the potential of frequent and prolonged use. Many such harms were identified in the setting of the SARS epidemic in 2003 and in the ensuing years and included respiratory fatigue, increased work of breathing, poor work capability, increased nasal resistance, fatigue with minimal workloads, elevated levels of carbon dioxide, facial dermatitis, acne and potential self-contamination events.³⁹⁻⁴⁴

Limitations

Though the trials in this review provide a reasonable body of evidence, there are several important limitations. First, there is considerable clinical heterogeneity between the designs, and substantial statistical heterogeneity for some analyses. The latter is not readily explained by differences in the study questions. Second, the range of viral infections studied is limited, with a particular focus on influenza; no studies include SARS-CoV-2. None of the studies in health care worker included undertaking aerosol-generating procedures for which WHO currently recommends the N95 or equivalent mask. Finally, the studies provide sparse and unsystematic data on any harms, such as the discomfort, dehydration, facial dermatitis, distress, headaches, exhaustion or other problems caused by masks such as the N95. Some studies measured adherence which was generally high despite the mask discomfort.

Conclusion

Despite the lack of evidence, we would still recommend using facial barriers in the setting of epidemic and pandemic viral respiratory infections, but there does not appear to be a difference between surgical and full respirator wear. Despite the methodological concerns, our review of the available studies demonstrates consistency in the finding of no difference between surgical and N95 or equivalent masks as a physical intervention to interrupt or reduce the spread of respiratory viruses, mainly influenza. The consistency of the finding across multiple studies of variable quality adds epidemiologic strength of association.

The fact that all included trials were conducted in relatively low transmission periods limits generalisability to an epidemic of the global size of COVID-19. We excluded in this part of the review trials testing the combination of hygienic and barrier methods. These have shown to be effective in observational studies carried out during the SARS 1 epidemic.⁸

Based on the evidence of the previous SARS epidemic large trials comparing full facial protection with surgical masks need to be carried out to settle the matter, given the difference in wearability, harms and costs. Funding for such trials and research once the epidemic has passed, is critical to inform future preparedness for global epidemics.

Disclosure

Tom Jefferson (TJ) was in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews (2015-018).

In 2014–2016, TJ was a member of three advisory boards for Boehringer Ingelheim. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine.

TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products for which he receives fees (current).

TJ was a member of three advisory boards for Boehringer Ingelheim (2014-16)

TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine (2015-2017).

TJ is a relator in a False Claims Act lawsuit on behalf of the United States that involves sales of Tamiflu for pandemic stockpiling. If resolved in the United States' favor, he would be entitled to a percentage of the recovery.

TJ is co-holder of a Laura and John Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project *Beyond Transparency in Pharmaceutical Research and Regulation* led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022).

TJ consults for Illumina LLC on next generation gene sequencing (2019-). TJ was the consultant scientific coordinator for the HTA Medical Technology programme of the Agenzia per i Servizi Sanitari Nazionali (AGENAS) of the Italian MoH (2007-2019).

TJ is Director Medical Affairs for BC Solutions, a market access company for medical devices in Europe (excluding devices relating to acute respiratory infections).

John Conly holds grants from the Canadian Institutes for Health Research, Alberta Innovates-Health Solutions and was the primary local Investigator for a *Staphylococcus aureus* vaccine study funded by Pfizer for which all funding was provided only to the University of Calgary for the conduct of the trial.

All other authors have no interests to declare.

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Dr Jefferson (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1: PRISMA Flow Diagram

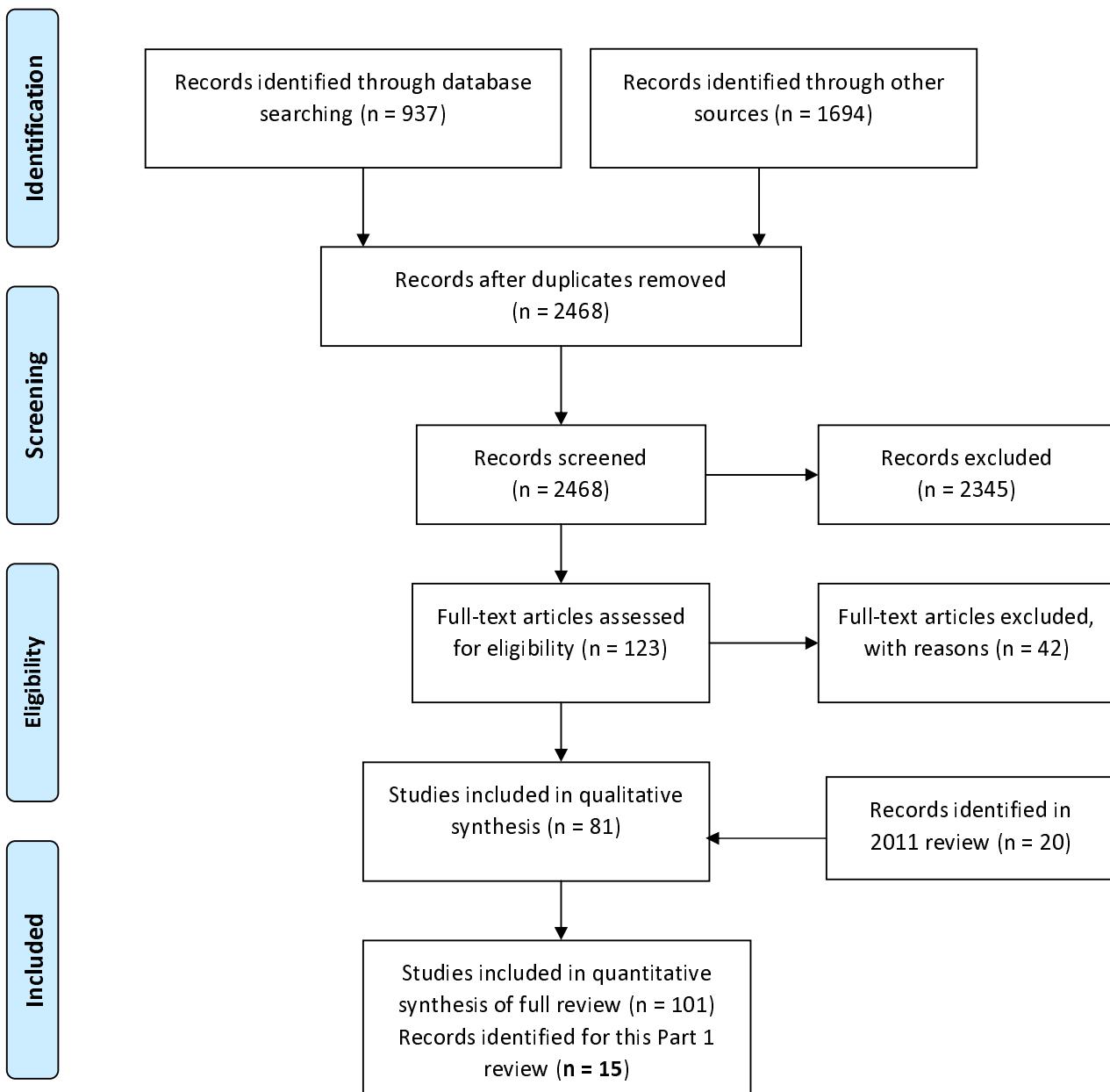


Figure 2. Risk of Bias in included studies - summary bar chart

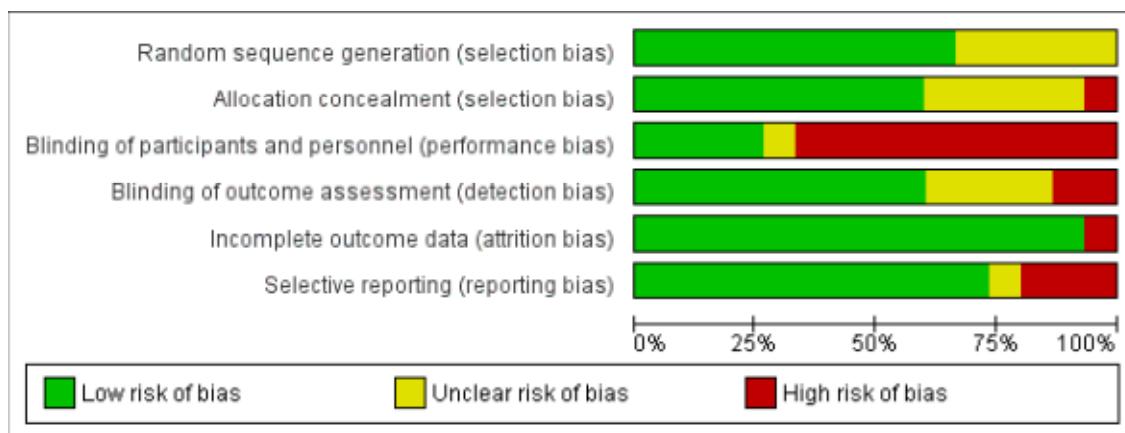


Figure 3a: Meta-analysis of trials comparing masks vs no masks in healthcare workers and in community populations: effect on rates of Influenza-like Illness (ILI) and laboratory-confirmed influenza

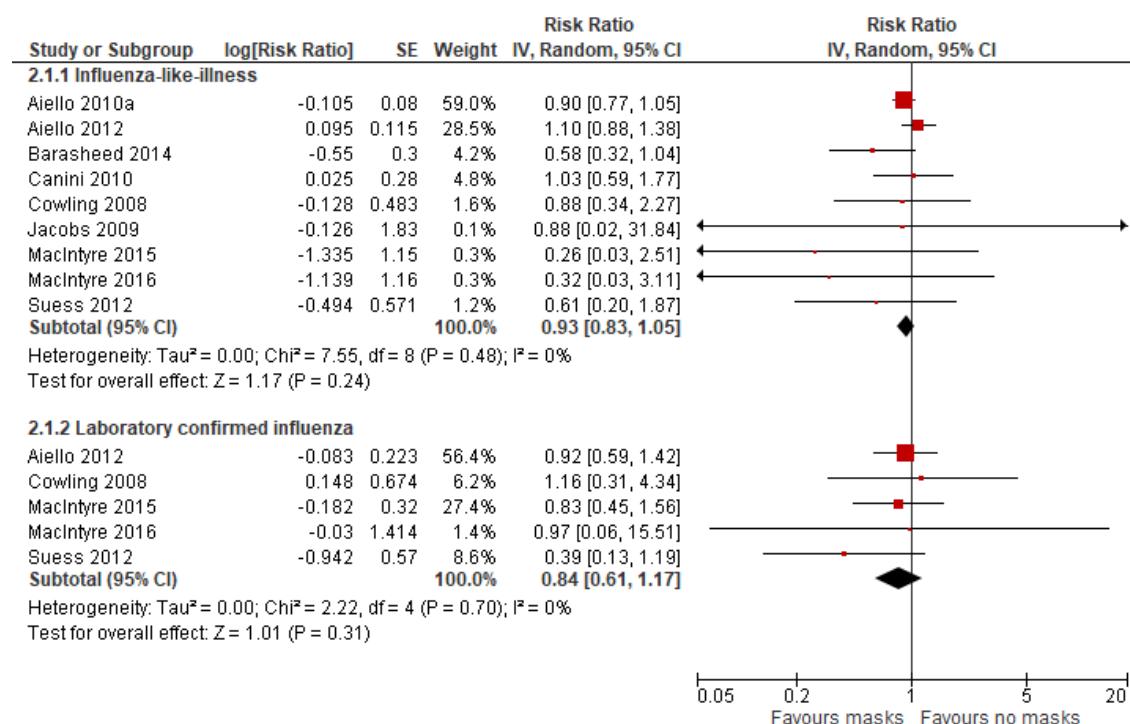


Figure 3b: Meta-analysis of trials comparing masks vs no masks in healthcare workers: effect on rates of Influenza-like illness (ILI)

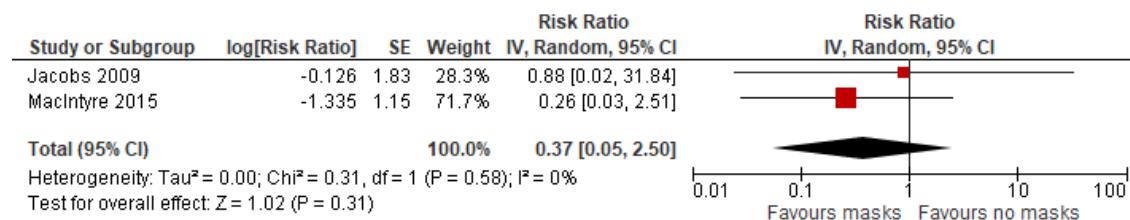
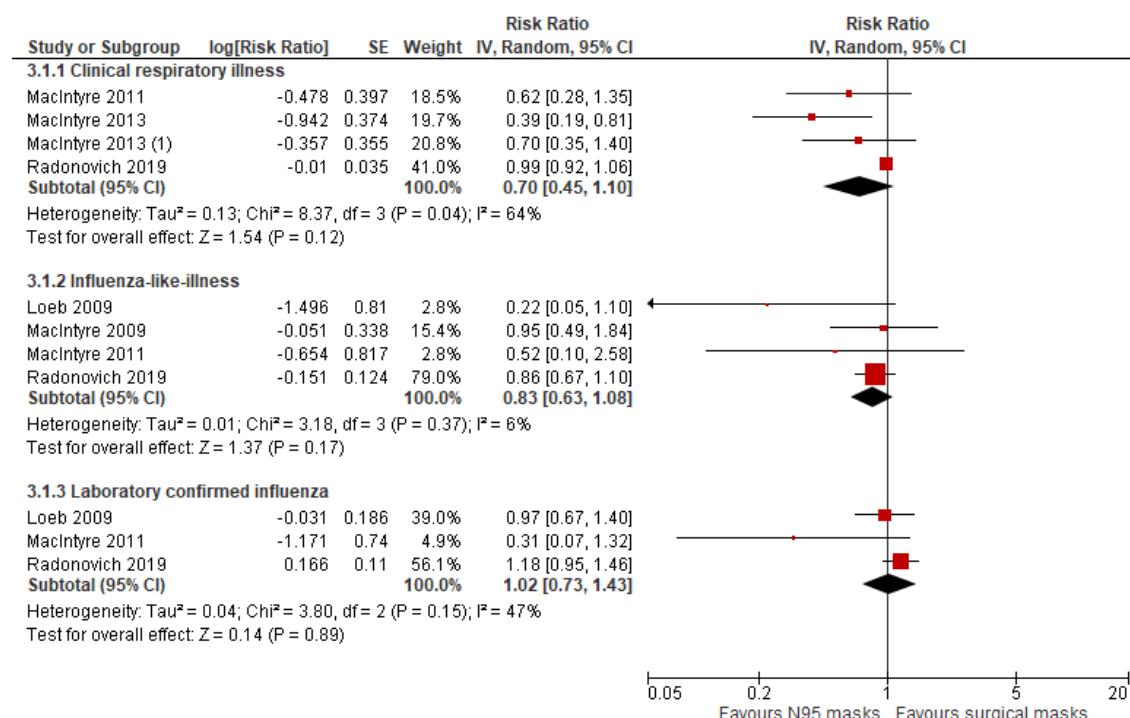


Figure 3c: Meta-analysis of trials comparing (surgical/medical) masks vs N95 respirators in healthcare workers and in community populations: effect on rates of clinical respiratory illness, Influenza-like Illness (ILI) and laboratory-confirmed influenza



Footnotes

(1) MacIntyre 2013 includes 2 comparisons: N95 vs surgical masks and targeted N95 vs surgical masks

Table 1 Description of interventions in included studies, using the items from the Template for Intervention Description and Replication (TIDieR) checklist

Author Year	Brief name	Recipient	Why	What (materials)	What (procedures)	Who provided	How	Where	When and how much	Tailoring	Modification of intervention throughout trial	Strategies to improve or maintain intervention fidelity	Extent of intervention fidelity
PERSON DISTANCING													
Miyaki 2011	Quarantine from work (Stay-at-home order)	Employees	Prevent spread of influenza in workplaces by quarantining workers who had a co-habitating family member with an influenza-like illness (ILI)	Full wages to employee	Non-compulsory asking of workers whose family members developed ILI to stay at home voluntarily on full wages. Daily measuring of temperature before leaving work. Where symptoms were doubtful, industrial physician made judgment. Company doctors provided input on cancelling of stay-at-home orders as required	Health management department oversaw the procedures and decisions	Mode of advice to employees not described	Car industries in Japan	Stay-at-home order for 5 days after resolution of ILI symptoms or 2 days after alleviation of fever over 7.5 months	Strict standard for cancelling of stay-at-home orders described	None described	Recording of compliance with stay-at-home request	100% compliance to stay at home reported
MASK AND HAND HYGIENE , either as stand-alone interventions or combined (for this part of the review, only data from the comparison of mask group vs control group were analysed)													
Aiello 2010a	2 active interventions: A. Face mask	Students living in university residences	Reduce the incidence of and mitigate influenza-	7 Face masks (standard medical procedure masks with ear loops TECNOL procedure	Weekly supply of masks through student mailboxes Provision of basic	Not described except education provided	Education via email and study	US University Residence Halls	One off education, 6 weeks (excluding	Mask wearing during sleep optional	University spring break occurs	Weekly web-based student survey included:	Average mask use hours/day : FM+HH

	(FM) B. Face mask and hand hygiene (FM+HH)	like illness (ILI) by use of non-pharmaceutical interventions (NPIs) of personal protection measures	masks; Kimberly-Clark) 7 Resealable plastic bags for mask storage when not in use (e.g. eating) and for disposal Alcohol-based hand sanitizer (62% ethyl alcohol in a gel base, portable 2 oz squeeze bottle, 8 oz pump) Hand hygiene education (proper hand hygiene practices and cough etiquette) via emailed video, study website, written materials detailing appropriate hand sanitizer and mask use	hand hygiene education through an email video link, the study website and written materials; instruction to wear mask as much as possible; education in correct mask use, change of masks daily, use of provided resealable bags for mask storage and disposal Provision of replacement supplies for which students signed for on receipt	via study website [URL not provided]. "Trained staff" for compliance monitoring Study-affiliated residence hall staff provided replacement supplies	website; provision of masks and sanitizer in person to residence		g spring break) of face mask and/or hand hygiene measures which commenced at "the beginning of the influenza season just after identification of the first case of influenza on campus" (p.496). Replacement supplies provided as needed	and encouraged outside of residence	ed during weeks 4 and 5 of the study, with most students leaving campus and travelling and were not required to continue protective measures in that time	self-reported average number of times hands washed / day and average duration of handwashing to obtain composite "optimal handwashing" score (at least 20 secs \geq 5 /day); average no of mask hours/day/ week; average hand sanitizer use / day / week and amount used.	2.99 vs 3.92 in FM Average handwashing times/day : FM+HH 6.11 vs 8.18 for FM vs 8.75 for control group Daily washing secs/day: FM+HH 20.65 vs 23.15 for FM vs 22.35 for control Hand sanitizer use times/day : FM+HH: 5.2 vs 2.31 for FM vs 2.02 for control No. of proper mask wearing participants / hour of observation
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												use	n: FM+HH: 2.26 FM: 1.94
Aiello 2012	2 interventions A. Face mask (FM) B. Face mask and hand sanitizer (FM+HH)	Students living in university residences	Prevent influenza-like illness (ILI) and laboratory confirmed influenza by use of non-pharmaceutical interventions (NPIs) of personal protection measures (e.g. face masks and hand hygiene).	Packets of 7 standard medical procedure masks with ear loops (TECNOL™ procedure masks, Kimberly-Clark, Roswell GA) and plastic bags for storage during interruptions in mask use (e.g., while eating, sleeping) and for daily disposal. Hand sanitizer (2 oz squeeze bottle, 8 oz pump bottle with 62% ethyl alcohol in a gel base). Replacement face masks and hand sanitizer. Educational video: proper hand hygiene and use of standard medical procedure face masks	Intervention materials and educational video provided Supply of masks and instructions on wearing Provision of replacement masks or sanitizers as needed on site	Trained study staff available at tables in each residence hall for surplus masks and sanitizer and for observing compliance	Hygiene packs delivered to student mailbox; face to face supply also available	US University Residence Halls	One off educational video at start Weekly supply of hygiene packs Masks to be worn at least 6 hours/day Study staff available on site with replacement supplies as needed for duration of intervention (6 weeks, excluding spring break)	Students encouraged but not obliged to wear masks outside of residence hall Majority of students left campus	1-week University spring break during the study when majority of students left campus	Weekly student survey including compliance (e.g. masks hours/day, frequency and amount of sanitizer use, number of hand washes/day, duration of hand washing (secs)) Observed compliance completed by trained study staff who daily and anonymously observed mask wearing in public areas of residences	Self-reported mask wearing: No significant difference Sanitizer use: Significantly more in FM+HH than FM or control groups. More results in S1. Staff observed an average of 0.0007 participants properly wearing a mask for each hour of observation
Cowling 2008	2 active interventions in addition to control of	Householders with confirmed index case with influenza-like-illness	Reduce transmission in households through non-pharmaceutu	A. Box of 50 surgical masks (Tecnol – The Lite One, Kimberly Clark, Roswell, GA) for each household member (or a box of 75 paediatric masks	A. Provision of masks and education in potential efficacy in reducing disease spread and demonstration of proper face mask	Home visit nurse provided interventions	Face to face to householders	Households in Hong Kong	9 days Initial home visit within 36 hours,	None described	None described	Home visit monitoring of adherence and interview day 9 about	Mask use: 45% (21%) M: reported often or always vs 30% (1%)

	healthy lifestyle education A. surgical face masks (M) B. hand hygiene (HH)	(ILL)	tical interventions	for children aged 3–7 years)	wearing and hygienic disposal B. Automatic alcohol hand sanitizer (WHO recommended formulation II, liquid content with 75% isopropyl alcohol, Vickmans Labs Ltd., Hong Kong), liquid hand soap (Avalon organics glycerin hand soap, Petaluma, CA), individual small (125 ml) bottles of alcohol hand gel (Gellygen gel with 70% ethyl alcohol, Brymore SA, Italy),	B. Education about the potential efficacy of proper hand hygiene in reducing transmission, distribution of automatic alcohol hand sanitizer, liquid soap and personal bottles and demonstration of hand hygiene and sepsis; instruction for all householders in when to use soap/sanitizer. Home visits to both groups to implement intervention All groups received healthy lifestyle education			then 3 visits on day 3, 6 and 9 A. Index subjects and all household contacts to wear masks as often as possible at home (except eating or sleeping) and when outside of the household B. use of liquid soap after every washroom visit and when hands were soiled, after sneezing or coughing; use sanitizer when first		adherence, count masks remaining / weigh amount of soap and alcohol left	in control and 28% (4%) in HH. Median mask use: index subjects: 12 masks Contacts: 6 Reported handwashing frequency : HH: 63% (41%) reported often or always vs 31% (27%) in control and 63% (47%) in mask Use (median): Sanitizer: 56g Liquid soap: 88g Bottles: Index: 7g Contacts: 5 g
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									returning home and immediately after touching any potentially contaminated surfaces					
Suess 2012	2 active interventions in addition to written information: A. Mask / Hygiene (MH) B. Mask (M)	Households with an influenza positive index case in the absence of further respiratory illness within the preceding 14 days	Prevent influenza transmission in households through easily applicable and accessible non-pharmaceutical interventions (NPI) - such as facemasks or hand hygiene measures	A. Alcohol based hand-rub (Sterilium™, Bode Chemie, Germany) A. and B. Surgical facemasks in two different sizes: Children < 14 years (Child's Face Mask, Kimberly-Clark, USA) and Adults (Aérokyn Masques, LCH Medical Products, France). Written information provided on correct use of intervention and on infection prevention (Seuss 2011) (Tips and information on the new flu A/H1N1) [URL provided is no longer active] Digital tympanic thermometer General written	A. Provision of hand-rub and masks A. and B. provision of masks only A. and B. Surgical facemasks in two different sizes: Children < 14 years (Child's Face Mask, Kimberly-Clark, USA) and Adults (Aérokyn Masques, LCH Medical Products, France). Written information provided on correct use of intervention and on infection prevention (Seuss 2011) (Tips and information on the new flu A/H1N1) [URL provided is no longer active] Digital tympanic thermometer General written	Study personnel arranged provision of materials, rang the participants, visited the homes, demonstrated and assessed fit of masks, Mask fit assessed (at first household visit) Information provided by telephone and written instructions at home visit on proper use of interventions and recommendations to sleep in a different room than the index patient, not to take meals with the index patient, etc (Seuss 2011) In person demonstration of interventions at first home visit	Provision of materials in person to households	Households in Berlin, Germany	Over 2 consecutive flu seasons	Adult masks worn if masks for under 14-year olds did not fit properly	In the season 2010/11 participants also recorded number of masks used per day	Self-reported daily adherence with facemasks, i.e. if they wore masks "always", "mostly", "sometimes", or "never" as instructed. Participants of the MH households additionally noted the number of hand disinfections per day.	Face mask use (median/individual): MH: 12.6 M: 12.9	Daily adherence was good, reaching a plateau of over 50% in nearly all groups from the third day on

			information on infection prevention	information on infection prevention				day of recruitment			NPI, the actual amount of used intervention materials and - if applicable - problems with wearing facemasks.	day
								Hand rub use: after direct contact with the index patient (or other symptomatic household members), after at-risk activities or contact ¹			Used intervention material per household member was calculated by dividing the amount used per household by the number of household members	See paper and Suess 2011 for more results

¹ having touched household items being used by the index patients and/or other symptomatic household contacts, and after coughing/sneezing, before meals, before preparing meals and when returning home

									Regular change of facemasks, not worn during the night or outside the household				
MASKS - compared to either no mask or different type of mask													
Barasheed 2014	Supervised mask use	Religious pilgrims ≥ 15 years	Prevent respiratory virus infections at mass gatherings through mask use	Plain surgical facemasks (3M™ Standard Tie-On Surgical Mask, Cat No: 1816) manufactured by 3M company, USA; 5 masks per day Written instructions on face mask use. Special polythene bags for disposal	Masks provided to index case and their contacts with advice on mask use (before prayers, in seminars and after meals) Written instructions provided on face mask use, need to change them and disposal	Not described, presumably the medical researchers	Face to face provision of masks, instructions and reminders	Tents of pilgrimage site (Mina Valley, Saudi Arabia)	Advice on mask use given throughout pilgrimage stay (5 days)	None reported	None reported	The medical researchers followed pilgrims each day to remind participants about recording their mask usage in health diary	Facemask use: Mask Group: 56/75 (76%), control group: 11/89 (12%) (p<0.001). 76% of intervention tents wore masks. 10 of 75 (13%) pilgrims in 'mask' tents wore facemasks during sleep.
Canini 2010	Surgical face masks	Householders (over 5 years)	Limit transmission of influenza transmission	Initial supply of 30 masks: For adults and children >10: Surgery masks with	Masks given immediately on home visit by attending GP with demonstration of proper use and	General practitioners	Face to face individually	Households in France	One off provision of masks worn for 5 days	None described	None described	Not described but reported mask usage	34 / 51 (66%) wore masks >80% of

			n by large droplets produced during coughing in households	earloops, 3 plys, anti fog (AEROKYN®, LCH medical products, Paris, France) Children 5-10: Face Mask KC47127, (Kimberly-Clark®, Dallas, TX, USA) Closed plastic bags for disposal	instruction to be worn for 5 days in presence of another household member or in confined space (e.g. car) and to change every 3 hours or if damaged						was measured	the duration. Reported mask-wearing: 11 ± 7.2 masks during 4.0 ± 1.6 days with an average use of 2.5 ± 1.3 masks per day and duration of use of 3.7 ± 2.7 hours/day	
Jacobs 2009	Face masks	Hospital healthcare providers (nurses, doctors and co-medical personnel)	Decrease risk of infection through limiting droplet spread through masks	Hospital-standard disposable surgical mask MA-3 (Ozu Sangyo, Tokyo, Japan); quantity not specified	Provision of masks and instructions for use	Not described presumably research team	Face to face	Tertiary care hospital in Tokyo, Japan Face masks worn while on hospital property	77 days	None described	None described	Self-reported compliance	Self-reported compliance for both groups reported as good with full compliance by 84.3% and remainder complying 79.2-98.7%
Loeb 2009	2 active interventions A. surgical masks B. N95	Healthcare workers (nurses)	Reduce transmission of influenza in healthcare settings through	A. Surgical masks B. N95 respirators	Provision of masks or N95 respirators Instruction in use and proper placement of devices	Provided by research team (not further described) Fit testing	In person face to face	Tertiary hospitals in Ontario, Canada Use of	1 influenza season (12 weeks)	Fit testing of nurses not already fit tested	Ceased before end of season	Compliance audits during peak of season by trained auditor who stood	18 episodes: N95: 6/7 participants (85.7%) wearing

	respirato rs		coughing or sneezing with protective masks		Fit testing and demonstration of positioning of N95 using standard protocol and procedure (details provided) Qualitative fit testing using saccharin or Bitrex protocol (OSHA, 2009)	by technician for N95		mask as required ² when providing care to or within 1 m of patient with febrile respirato ry illness, ≥38°C and new or worsenin g cough or shortness of breath Nurses to wear N95 when caring for patients with “febrile respirato ry illness”			short distance from patient isolation room	assigned device vs 100% for masks	
MacIntyre 2009	2 active interventions in addition to infection control guidelines	Householders with a child with fever and respiratory symptoms	Prevent or reduce respiratory virus transmission in the community through nonpharm	A. 3M surgical mask, catalogue no. 1820; St. Paul, MN, USA for adults B. P2 masks (3M flat-fold P2 mask, catalogue no. 9320;	Provision of masks and pamphlets and education about infection prevention and mask use Telephone calls and exit interviews to record adherence to	Not described presumably research team	Face to face and by telephone	Households in Sydney, Australia	2 winter seasons (3 months and 6 months) 2 weeks of follow-	None described	None described	Daily telephone calls to record mask use throughout day Exit	Reported mask use: Day 1 SM: 36/94 (38%) P2: 42/92 (46%) stated wearing

² Preventing respiratory illnesses: protecting patient and staff: infection control and surveillance standards for febrile respiratory illness (FRI) in nonoutbreak conditions in acute care hospitals [September 2005]. Ministry of Health and Long-Term Care, Public Health Division, Provincial Infectious Diseases Advisory Committee. http://www.health.gov.on.ca/english/providers/program/infectious/diseases/best_prac/bp_fri_080406.pdf. Accessed September 11, 2009.

	A. surgical masks (SM) B. P2 masks (P2)		aceutical interventions	Bracknell, Berkshire, UK) A and B: Health guidelines and pamphlets about infection control	mask use All groups: Health guidelines, pamphlets about infection control were provided			up Masks to be worn at all times when in same room as index child, regardless of distance from child			interviews about adherence	"most or all" of the time. Other participants were wearing face masks rarely or never. Day 5: SM: 29/94 (31%) P2: 23/92 (25%)	
MacIntyre 2015	2 active interventions A: Cloth masks B: Medical masks	Hospital healthcare workers (HCWs)	Prevent respiratory infections in healthcare workers from patients through mask-wearing	A. 5 cloth masks for study duration (2-layer, cotton) B. 2 medical masks daily for each 8-hour shift for study duration (3 layers, non-woven material) All masks locally manufactured Written instructions on cleaning cloth masks	Cloth or medical masks to be worn at all times on shift Cloth masks to be washed with soap and water daily after shifts and the process of cleaning to be documented Provision of written instructions for cloth mask cleaning	Researchers arranged supply of masks and instructions and any training of staff assisting the delivery	Masks and written instructions provided face to face	Hospital wards in Vietnam	4 weeks (25 days) of facemasks use	Masks not worn while in the toilet or during tea or lunch breaks	None described	Monitored compliance with mask use by self-report diary card and exit survey and interviews with a sub-sample (ACTRN12610000887077)	Mask wearing compliance: Cloth mask: 56.8%; Medical mask: 56.6% Reported cloth mask washing: 23/25 days (92%)
MacIntyre 2011	3 active interventions A. medical masks B. N95 respirators fit-tested C. N95 respirators non-	Healthcare workers (HCWs)	Protect HCWs by preventing transmission of influenza and other respiratory viruses from patients through mask	Daily supply of A. 3 medical masks (3M™ medical mask, catalogue number 1820, St Paul, MN, USA) 2 respirators: B. N95 fit-tested mask (3M™ flat-fold N95 respirator, catalogue number 9132) fit-tested with	Supply of masks or respirators. Instruction in when to wear it, correct fitting and storage (in paper bag in personal locker) Instruction in importance of hand hygiene before and after removal For fit-tested group:	Masks provided to hospitals Training of staff provided by one of research team	Masks and training provided face to face, not described if training was individually or in groups	Emergency departments and respiratory wards in hospitals in Beijing, China	Entire work shift for 4 weeks	Taken off for toilet and meal breaks and end of shift	None described	Mask / respirator use monitored by: (i) observed compliance by head ward nurse recorded daily (ii) self-report diary	Adherence for usage was high for all and not significantly different in all arms. Medical mask: 76%, 5

	fit-tested		wearing	3M™ FT-30 Bitrex Fit Test kit according to manufacturers' instructions (3M™, St Paul, MN, USA). C. N95 nonfit-tested mask (3M™ flat-fold N95 respirator, catalogue number 9132) Diary cards for usage recording	fit-testing procedure							cards carried during day recording (i) no. hours (ii) usage. Exit interviews	hours; N95 fit-tested: 74%, 5.2 hours; N95 nonfit-Tested: 68%, 4.9 hours.
MacIntyre 2013	3 active interventions A. N95 respirators at all times B. N95 respirators targeted use C. medical masks	Healthcare workers (nurses and doctors)	Protect healthcare workers from respiratory infections from patients through mask use	Daily supply of: A. and B. 2 respirators (3M Health Care N95 Particulate Respirator; catalog number 1860; 3M) 3M FT-30 Bitrex Fit Test Kit C. 3 masks 3 masks (3M Standard Tie-On Surgical Mask catalog number mask 1817; 3M, St. Paul, MN) Pocket-sized diary card with tick boxes for mask use	Supply of respirators Instructions in use including times and fit Fit testing procedure according to the manufacturer's instructions (3M) For targeted N95: checklist of defined high-risk procedures, including common aerosol-generating procedures	3M supplied respirators and masks Provider of instructions not specified	Masks and training provided face to face, not described if training was individually or in groups	Emergency departments and respiratory wards of tertiary hospitals in Beijing, China	For 4 weeks, A and B worn at all times on shift; B. targeted (intermittent) use of N95 respirators only while doing high-risk procedures or barrier	None described	None described	Self-reported daily record of number of hours worked, mask or respirator use, number of high-risk procedures undertaken collected by study staff	Compliance highest for targeted N95 (82%; 422/516), vs N95 (57%; 333/581) vs medical mask (66%; 380/572)
MacIntyre 2016	Medical mask use	Sick householders with ILI (index cases) and their well contacts of the same household	Protect well people in the community from transmission of respiratory pathogens by contacts with	21 medical masks (3M 1817 surgical mask). Diary cards for mask use	Supply of masks Instructions for mask wearing and handwashing protocol Provision of diary cards	Study staff member provided masks instructions in use	Masks and instructions provided face to face and individually	Fever clinics of major hospitals in Beijing, China	3 masks / day for 21 days Mask wearing: Whenever in the same room as a	Allowed to remove their masks during mealtimes and while asleep and to	None reported	Self-reported daily record of mask use using diary card	Mask use: Mask group: 4.4 hours, control group: 1.4 hours

Radonovich 2019	2 active interventions A. N95 respirators (N95) B. medical masks (MM)	Health care personnel (HCP) of outpatient sites within medical centres	influenza-like illness (ILI) through mask use	A. N95 respirators: 3M Corporation 1860, 1860S, and 1870 (St Paul, Minnesota) or Kimberly Clark Technol Fluidshield PFR95-270, PFR95-274 (Dallas, Texas) B. Medical mask Precept 15320 (Arden, North Carolina) or Kimberly Clark Technol Fluidshield 47107 (Dallas, Texas). Reminder signs posted at each site A portable computer equipped with data recording software (HandyAudit; Toronto, Canada) to document adherence (Radonovich 2019b)	Participants instructed to wear assigned protective devices whenever they positioned within 6 feet (1.83m) of patients with suspected or confirmed respiratory illness and to don a new N95 / MM with each patient interaction Hand hygiene recommended to all participants in accordance with Centers for Disease Control and Prevention guidelines Infection prevention policies were followed at each study site Reminder signs posted at sites and emails sent	Centres provided device to HCP supplied by study Study personnel posted reminder signs and emails and conducted adherence observations	Face to face individual provision of devices and adherence observations On site posting of signs Other reminders by email	Outpatient sites within medical centres in US	household member or a visitor to the household. Hand washing: before putting on and after taking off As instructed, for each new patient interaction during 12-week period of peak viral respiratory illness each year for 4 years (total of 48 weeks)	cease wearing once symptoms resolved	Fitting of N95 masks None described	Reminder signage posted at study sites and emails sent by study personnel Self-reported daily device wearing of "always," "sometimes," "never," or "did not recall." Observation of device-wearing behaviours as participants entered and exited care rooms conducted during unannounced visits	Device wearing: N95: 89.4% reported "always" or "sometimes" vs Mask: 90.2% "Never" N95: 10.2% MM: 9.5%

					Annual fit testing conducted for all participants Filtration testing performed on the device models in the study. Further details in protocol (Radonovich 2016)						ed, inconspicuous visits to randomly selected sites documented on portable computer	
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Additional references used to provide information in the table

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Table 2: Characteristics of included studies

PERSON DISTANCING	
Miyaki 2011	
Method	A quasi-cluster randomized controlled trial
Participants	A total of 15,134 general employees (age, 19–72 yr old in 2009) of two sibling companies of major car industry in Kanagawa Prefecture, Japan. All workers who regularly reported to be the workplace were included, regardless of treatment for chronic diseases. All employees have the same health insurance plan and followed up in the same way
Interventions	See table 1
Outcomes	<p>Workroom: influenza A test kit (rapid test)</p> <p>Effectiveness: Assess the effectiveness of household-quarantine in reducing the incidence of influenza A H1N1. ILI was defined as a body temperature greater than 38°C or more than 1°C above the normal temperature accompanied with more than two of these symptoms: nasal mucus, pharyngeal pain, cough, chills or heat sensation</p> <p>Safety: The incidence of influenza A H1N1 among workers who were told to stay home if a family member developed ILI was higher (relative risk of 2.17 $p<0.001$) compared to control group. No other safety measures /harms reported</p>
Notes	<p>Period study conducted: July 1, 2009 to February 19, 2010</p> <p>Funding: Unfunded</p> <p>Compliance: Our intervention was not compulsory; we only asked the employees to leave the workplace for a while on full pay, and we succeeded in getting all workers' agreement. In our case, explaining that the home waiting policy might be beneficial to the whole workers and help to avoid stopping the manufacturing lines (explaining it is for the benefit of the public) and guaranteeing payment during the leave (financial support) helped them to obey our request.</p>
MASK AND HAND HYGIENE , either as stand-alone interventions or combined (for this part of the review, only data from the comparison of mask group vs control group were analysed)	
Aiello 2010a	
Method	<p>Cluster-randomised trial assessing the effects of hand sanitiser and masks with masks or no intervention on ILI symptoms. The trial was conducted in University halls of residence with more than 100 student residents in a US university during the 2006 to 2007 influenza "season". It lasted 6 weeks</p> <p>The units of randomisation were 7 of the 15 halls. One hall was very large (1240 residents) and the 6 remaining ones which had between 110 and 830 residents were combined into 2 clusters roughly equivalent in size. The 3 clusters were then randomised by random extraction of the clustered halls' names out of a container. The largest hall (single-cluster) was randomised to the mask and hand sanitiser arm, the 4 halls cluster received masks and the remaining 2 halls were assigned as controls.</p>
Participants	Willing, consenting residents aged 18 or more. Recruitment of students began in November 26 but the trial did not go "live" with distribution of intervention materials until 22 January 2007 when the first case of influenza was confirmed on campus by laboratory tests. Enrolment continued until 16 February 2007 and the study was completed on 16 March 2007. During the study period there

	was a 1-week break when the majority of residents left campus. There were 1327 eligible participants, of which 1297 had a complete baseline survey and at least 1 weekly survey result (367, 378 and 552 in the mask and hand sanitiser, mask only and control groups respectively, giving a total of 1297). It is unclear what the ineligibility criteria were for the 30 missing (1327 minus 1297) but the explanation may be in the appendix.
Interventions	See table 1
Outcomes	Laboratory details are described in appendix Effectiveness: ILI, defined as cough and at least 1 constitutional symptom (fever/feverishness, chills, headache, myalgia). ILI cases were given contact nurses phone numbers to record the illness and paid USD 25 to provide a throat swab. 368 participants had ILI and 94 of these had a throat swab analysed by PCR. 10 of these were positive for influenza (7 for A and 3 for B), respectively by arm 2, 5 and 3 using PCR, 7 using cell culture Safety: not reported
Notes	The authors conclude that "These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1) pandemic". This conclusion is based on a significantly lower level of ILI incidence in the mask and hand sanitiser arm compared to the other 2 arms after adjustment for covariates (30% to 50% less in arm 1 compared to controls in the last 2 weeks of the study) Comparison with the ILI rate of the control arm may not be a reflection of the underlying rate of ILI because the intervention arm received instruction on hand sanitation and hand etiquette. The play of adjustments is unclear. The intra cluster correlation coefficient is reported in the footer of Table 4. Its very small size suggests lack of clustering within halls. The role of the spring break is mentioned in the Discussion as are the results of this study compared to other studies included in our review (Cowling 2008 and MacIntyre 2009) The authors report that 147 of 1297 participants (11.3%) "at baseline" had ILI symptoms and were excluded from analysis. During the 6 weeks of the study 368 of 1150 participants (32%) had ILI. This averages out at about 5% per week. It is unclear what the term "at baseline" means. Presumably this means during the 2 to 3 weeks of participant enrolment. If this is so, the reason for the triggering of the interventions (tied to influenza isolation) are obscure as the trial is supposedly about ILI and an ILI outbreak was already underway "at baseline"
Aiello 2012	
Method	During the 2007-08 influenza season, 1,111 students residing in university residence halls were cluster randomized by residence house (N = 37) to either face mask and hand hygiene, face mask only, or control arms. Discrete time survival analysis using generalized models estimated rate ratios, according to study arm, each week and cumulatively over the 6-week intervention period, for clinically verified ILI and laboratory-confirmed influenza A or B.
Participants	1187 young adults living in 37 residence halls, which were randomly assigned to 1 of 3 groups— face mask use (n 392), face masks with hand hygiene (n 349), or control (n 370)— for 6 weeks.
Interventions	See table 1
Outcomes	Clinically verified ILI - case definition (presence of cough and at least one or more of fever/feverishness, chills, or body aches) Laboratory-confirmed influenza A or B. Throat swab specimens were tested for influenza A or B using real-time polymerase chain reaction (Rt-PCR). No safety outcomes reported
Notes	This study has the same trial registration number as the Aiello 2010 study; Study funded by government and pharmaceutical

	industry
Cowling 2008	
Method	Cluster-randomised controlled trial carried out in Hong Kong SARS between February and September 2007. The study assessed the effects of non-pharmaceutical interventions on the household transmission of influenza over a 9-day period. ILI cases whose family contacts had been symptom-free for at least 2 weeks rapid tested for influenza A and B were used and randomised to 3 interventions carried out. Randomisation was carried out in 2 different schedules (2:1:1 for the first 100 households and subsequently 8:1:1) but it is unclear why and how
Participants	946 index subjects aged 2 years or more in 122 clusters (households). 116 households were included in the analysis, 6 were excluded because subsequent laboratory testing (culture) were negative. There were 350 household contacts in the analysis but there 370 household contacts at randomisation. Attrition is not explained. Index cases were defined as subjects presented with at least 2 influenza-like symptoms of at least 48 hour duration (such as fever more or equal to 38 degrees, cough, headache, coryza , sore throat, muscle aches and pains) and positive influenza A+B rapid test
Interventions	See table 1
Outcomes	Laboratory: QuickVue RTI MDCK culture Samples were harvested using NTS, but the text refers to a second procedure from June 2007 onwards testing for non-influenza viruses but no data were reported Effectiveness: secondary attack ratios (SAR): SAR is the proportion of household contacts of an index case who subsequently were ill with influenza (symptomatic contact individuals with at least 1 NTS positive for influenza by viral culture or PCR) Three clinical definitions were used for secondary analysis: 1. Fever more or equal to 38 degrees or at least 2 of following symptoms, headache, coryza , sore throat, muscle aches and pains 2. At least 2 of the following S/S: fever more or equal to 37.8 degrees, cough, headache, sore throat and muscle aches and pains 3. Fever of more or equal to 37.8 degrees plus cough or sore throat Safety: no harms were reported in any of the arms
Notes	The authors conclude that "The secondary attack ratios were lower than anticipated, and lower than reported in other countries, perhaps due to differing patterns of susceptibility, lack of significant antigenic drift in circulating influenza virus strains recently, and/or issues related to the symptomatic recruitment design. Lessons learnt from this pilot have informed changes for the main study in 2008" Although billed as a pilot study the text is highly confusing and at times contradictory. The intervention was delivered at a home visit up to 36 hours after the index case was seen in the outpatients. This is a long time and perhaps the reason for the failure of the intervention. Practically, the intervention will have to be organised before even seeking medical care – i.e. people know to do it when the kid gets sick at home
Suess 2012	
Method	Cluster randomised controlled trial, open-label, parallel design
Participants	Patients presenting to general practitioners or family physicians at the study sites within 2 days of symptom onset, had a positive rapid antigen test for influenza (later to be confirmed by quantitative Reverse Transcription Polymerase Chain Reaction [qRT-

	PCR]), and were at least 2 years old. Index cases also had to be the only household member suffering from respiratory disease within 14 days prior to symptom onset. Exclusion criteria were pregnancy, severely reduced health status and HIV infection. One person households were also not eligible or inclusion
Interventions Outcomes	<p>See table 1</p> <p>Primary outcomes: SAR of Lab-confirmed (qRT-PCR) influenza infection among household members (Secondary infection cases) presenting with ILI within the observation period (8 days from the date of onset). ILI was defined as fever ($>38.0^{\circ}\text{C}$ + cough or sore throat). Nasal wash specimens (or - if these were not possible - nasal swabs) from all participating household members.</p> <p>Effectiveness Secondary outcomes: laboratory-confirmed influenza infection in a household contact (Secondary infection cases). We defined a symptomatic secondary influenza virus infection as a laboratory-confirmed influenza infection in a household member who developed fever ($>38.0^{\circ}\text{C}$), cough, or sore throat during the observation period. We termed all other secondary cases as subclinical. A secondary outcome measure was the occurrence of ILI as defined by WHO as fever plus cough or sore throat.</p> <p>Safety: Study reported the majority of participants (107/172, 62%) did not report any problems with mask-wearing. This proportion was significantly higher in the group of adults (71/100, 71%) compared to the group of children (36/72, 50%) ($p = 0.005$). The main problem stated by participants (adults as well as children) was "heat/humidity" (18/34, 53% of children; 10/29, 35% of adults) ($p = 0.1$), followed by "pain" and "shortness of breath" when wearing a facemask.</p>
Notes	<p>Period study conducted: Nov 2009 to Apr 2011</p> <p>Funding: Governmental</p> <p>Adherence: In general, daily adherence was good, reaching a plateau of over 50% in nearly all groups (M and MH groups; 2009/10 and 2010/11) from the third day on (by then the intervention had been implemented in all households). A gradual decline towards lower adherence began around the sixth day of the index patient's illness.</p>
MASKS - compared to either no mask or different type of mask	
Barasheed 2014	
Method	Pilot, non-blinded, parallel, cluster-randomised trial
Participants	Australian pilgrims with the following criteria. Inclusion criteria for Index Case: 1) Australian pilgrims of any gender aged >15 years who attend the Hajj 2011 and 2) have symptoms of respiratory infection for ≥ 3 days. For close tent contact: 1) Australian pilgrims of any gender aged 15 years or more who attend the Hajj 2011, and 2) pilgrims who share the same tent and sleep 'immediately close' to the index case. Exclusion Criteria: for index case: 1) pilgrims who do not suffer from symptoms of respiratory infection, 2) pilgrims who present with symptoms of respiratory infection for > 3 days and 3) children aged less than 15 years. For close tent contact: 1) pilgrims who are symptomatic at presentation, 2) pilgrims who are not close tent contacts of an index case and 3) children aged less than 15 years. Only 10% - 15% of potential participants took part in the study.
Interventions Outcomes	<p>See table 1</p> <p>Laboratory: Two nasal swabs from all ILI cases and contacts. One for influenza point of care testing (POCT) using the QuickVue</p>

	<p>Influenza (A+B) assay (Quidel Corporation, San Diego, USA) and one for later nucleic acid testing (NAT) for influenza and other respiratory viruses. But there was a problem with getting POCT on time during Hajj.</p> <p>effectiveness: to assess the effectiveness of face masks in the prevention of transmission of influenza-like illness (ILI). ILI was defined as subjective (or proven) fever plus one respiratory symptom (e.g. dry or productive cough, runny nose, sore throat, shortness of breath).</p> <p>Safety: None planned or reported</p>
Notes	<p>The period study conducted: 4-10 November 2011</p> <p>Funding: Government (Qatar National Research Fund (QNRF))</p> <p>Compliance: with facemask use by pilgrims in the 'mask' group was 56 of 75 (76%), while it was 11 of 89 (12%) in the 'control' group ($p<0.001$). The proportion of facemask user in the 'mask' tents was 76% for both males (19/25) and females (38/50). The most often reported reason for not wearing facemasks was discomfort (15%).</p>
Canini 2010	
Method	<p>A cluster randomized intervention trial conducted in France during the 2008–2009 influenza season. Households were recruited during a medical visit of a household member with a positive rapid influenza A test and symptoms lasting less than 48 hours. Households were randomized either to the mask or control group for 7 days. In the intervention arm, the index case had to wear a surgical mask from the medical visit and for a period of 5 days. The trial was initially intended to include 372 households but was prematurely interrupted after the inclusion of 105 households (306 contacts) following the advice of an independent steering committee. Generalized estimating equations were used to test the association between the intervention and the proportion of household contacts who developed an influenza-like illness during the 7 days following the inclusion.</p>
Participants	The study was conducted in 3 French regions (Ile de France, Aquitaine and Franche-Comte') and included households of size 3 to 8. 105 households were randomised, which represented 148 contacts in the intervention arm and 158 in the control arm.
Interventions	See table 1
Outcomes	<p>The primary endpoint was the proportion of household contacts who developed an ILI during the 7 days following inclusion. Exploratory cluster level efficacy outcome, the proportion of households with 1 or more secondary illness in household contacts. A temperature over 37.8°C with cough or sore throat was used as primary clinical case-definition.</p> <p>Adverse reactions due to mask-wearing</p>
Notes	Government funded
Jacobs 2009	
Method	<p>Open randomised controlled trial lasting 77 days from January 2008 to test "superiority" of face masks in preventing URTI. This term appears as an acronym in the introduction and is not explained. It is assumed it stands for "upper respiratory infections" but it is preceded in the text by the term "common cold" which is also lacking a definition. Randomisation was carried out in blocks within each of 3 professional figures (physicians, nurses and "co-medical" personnel)</p>
Participants	<p>33 HCWs mainly females aged around 34 to 37 in a tertiary healthcare hospital in Tokyo, Japan. HCW with "predisposing conditions" (undefined) to "URTI" and those taking antibiotics were excluded</p> <p>A baseline descriptive survey was carried out including "quality of life"</p> <p>1 participant dropped out at end of week 1 but no reason is reported nor the allocation arm</p>
Interventions	See table 1
Outcomes	Laboratory; n/a

	Effectiveness: URTI is defined on the basis of a symptoms score with a score >14 being a URTI according to Jackson's 1958 criteria ("Jackson score"). These are not explained in text although the symptoms are listed in Table 3 (any, sore throat, runny nose, stuffy nose, sneeze, cough, headache, ear ache, feel bad) together with their mean and scores SD by intervention arm Safety: the text does not mention or report harms. These appear to be indistinguishable from URTI symptoms (e.g. headache which is reported as of significantly longer duration in the intervention arm). Compliance is self-reported as high (84.3% of participants)
Notes	The authors conclude that "Face mask use in healthcare workers has not been demonstrated to provide benefit in terms of cold symptoms or getting colds. A larger study is needed to definitively establish non-inferiority of no mask use" This is a small, badly reported trial. The purpose of trials is to test hypotheses not to prove or disprove "superiority" of interventions. There is no power calculation and CIs are not reported (although there is a mention in Discussion). No accurate definitions of a series of important variables (e.g. URTI, runny nose etc.) are reported and the Jackson scores are not explained, nor their use in Japanese personnel or language validated.
Loeb 2009	
Method	Open non-inferiority randomised, controlled trial carried out to compare the surgical mask with the N95 respirator in protecting healthcare workers against influenza. The trial was carried out between 2008 (enrolment started in September and follow up on 12 January 2009) and 23 April 2009 (when all HCWs were told to wear a N95 respirator for all HCWs caring for febrile patients because of the appearance of novel A/H1N1). The trial trigger was the beginning of the influenza season defined as isolation of 2 or more viruses in a district in the same week. Following the 2003 SARS outbreak all Ontario nurses caring for febrile patients (38 °C or more and new onset cough or SOB) had to wear surgical masks. The randomisation (carried out in blocks of 4 by centre) then consisted of either confirmation to same-maker surgical mask wear or N95 respirator wear. Investigators and laboratory staff were blind to allocation status, but for obvious reasons (the visible difference in interventions), participants were unblinded. "The criterion for non-inferiority was met if the lower limit of the 95% confidence interval (CI) for the reduction in incidence (N95 respirator minus surgical group) was greater than -9%". So this is the non-inferiority margin. It is assumed that the "minus surgical group" means minus surgical mask group.
Participants	Consenting nurses (n = 446 randomised) aged a mean of 36.2 years working full time (\geq 37 hours/week) in 23 acute units (a mix of paediatric, A&E and acute medical units) in 8 hospitals in Ontario, Canada. 225 were randomised to the surgical mask and 221 to the N95 respirator. There were 13 and 11 dropouts respectively from each arm (all accounted for) plus 21 and 19 lost to follow up. 11 in each arm gave no reason, the others are accounted for. There were no deaths. The final total of 212 and 210 was included in the analysis. Table 1 reports the demographic data of participants by arm, which appear comparable.
Interventions	See table 1
Outcomes	Laboratory RT-PCR paired sera with 4-fold antibody rise from baseline (only for unvaccinated) nurses Effectiveness: follow up (lasting a mean of around 97 days for both arms) was carried out twice-weekly on a web-based instrument. Nurses with new symptoms were asked to swab a nostril if any of the following signs or symptoms had developed: fever (temperature \geq 38°C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, earache, ear infection or chills The text defines influenza with laboratory-confirmation and separately reports criteria for swab triggering and a definition of <u>ILI</u> ("Influenza-like illness was defined as the presence of cough and fever: a temperature \geq 38°C"). But this is not formally linked to influenza in the text as it appears that primary focus was the detection of laboratory-confirmed influenza (either by RT-PCR or

	<p>serology)</p> <p>Additional outcome data sought were work-related absenteeism and physician visits for respiratory illness</p> <p>Secondary outcomes included detection of the following non-influenza viruses by PCR: parainfluenza virus types 1, 2, 3 and 4; respiratory syncytial virus types A and B; adenovirus; metapneumovirus; rhinovirus-enterovirus; and coronaviruses OC43, 229E, SARS, NL63 and HKU1</p> <p>Audits to assess nurse compliance with the interventions were carried out in the room of each patient cared for. The text reports that 50 and 48 nurses in the surgical mask and N95 groups respectively had laboratory confirmation of influenza infection, indicating non-inferiority. Interestingly non-inferiority seemed to be applicable both to seasonal viruses and nH1N1 viruses (as 8% and 11.9% were serologically positive to nH1N1). This finding is explained either by seeding or cross reaction with seasonal H1N1. Equivalent conclusions could be drawn for nurses with complete follow up. Non-inferiority was applicable also to other ILI agents identified. None of the 52 persons with positive isolates met the criteria for ILI</p> <p>All cases of ILI were confirmed as having influenza (9 and 2 respectively). This means that all the 11 cases of ILI had influenza but that most of those with a laboratory diagnosis of influenza did not have cough and fever. For example the text reports that "Of the 44 nurses in each group who had influenza diagnosed by serology, 29 (65.9%) in the surgical mask group and 31 (70.5%) in the N95 respirator group had no symptoms". By implication of the 88 nurses with antibody rises 28 had symptoms of some kind, i.e. two-thirds were asymptomatic. Absenteeism was 1 versus 39 episodes in the mask versus respirator arms. No episodes of LRTI were recorded. The number of family contacts with ILI were the same for each arm (45 versus 47). Physician visits were similar in both groups</p> <p>Safety: no AEs are reported</p>
Notes	<p>The authors conclude that "Among nurses in Ontario tertiary care hospitals, use of a surgical mask compared with a N95 respirator resulted in non-inferior rates of laboratory-confirmed influenza"</p> <p>This a well-designed and conducted trial with credible conclusions. The only comment is that the focus in the analysis on influenza (symptomatic and asymptomatic) is not well-described, although the rationale is clear (interruption of transmission)</p>
MacIntyre 2009	
Method	Prospective cluster-randomised trial carried out in Sydney, Australia, to assess the use of surgical masks, P2 masks and no masks in preventing influenza-like illness (ILI) in households. The study was carried out during the 2 winter seasons of 2006 and 2007 (August to the end of October 2006 and June to the end of October 2007). "Gaussian random effects were incorporated in the model to account for the natural clustering of persons in households"
Participants	290 adults from 145 families; 47 households (94 enrolled adults and 180 children) were randomised to the surgical mask group, 46 (92 enrolled adults and 172 children) to the P2 mask group, and 52 (104 enrolled adults and 192 children) to the no-mask (control) group
Interventions Outcomes	<p>See table 1</p> <p>Laboratory: serological evidence</p> <p>Effectiveness: Influenza-like illness (ILI) (described as fever, history of fever or feeling feverish in the past week, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, headache).</p> <p>However, a positive laboratory finding for influenza converts the ILI definition into one of influenza.</p> <p>Safety: not reported</p>
Notes	The authors conclude that adherence to mask use significantly reduced the risk for ILI-associated infection, but < 50% of

	<p>participants wore masks most of the time. We concluded that household use of face masks is associated with low adherence and is ineffective for controlling seasonal respiratory disease. Compliance was by self-report – therefore likely to be an underestimate. The primary outcome was ILI or lab-positive illness. This showed no effect. Sensitivity analysis by adherence showed that under the assumption that the incubation period is equal to 1 day (the most probable value for the 2 most common viruses isolated, influenza (21) and rhinovirus (26)), adherent use of P2 or surgical masks significantly reduces the risk for ILI infection, with a hazard ratio equal to 0.26 (95% CI 0.09 to 0.77; P = 0.015). No other covariate was significant. Under the less likely assumption that the incubation period is equal to 2 days, the quantified effect of complying with P2 or surgical mask use remains strong, although borderline significant; hazard ratio was 0.32 (95% CI 0.11 to 0.98; P = 0.046). The study was underpowered to determine if there was a difference in efficacy between P2 and surgical masks (Table 5). The study conclusion appears to be a post-hoc data exploration. Regardless of this the study message is that respirator use in a family setting is unlikely to be effective as compliance is difficult unless there is a situation of real impending risk</p>
MacIntyre 2015	
Method	A cluster randomised trial of cloth masks compared with medical masks in healthcare workers in 14 secondary-level/tertiary-level hospitals in Hanoi, Vietnam. Hospital wards were randomised to: medical masks, cloth masks or a control group (usual practice, which included mask wearing). Participants used the mask on every shift for 4 consecutive weeks.
Participants	1607 hospital HCWs aged ≥ 18 years working full-time in selected high-risk wards.
Interventions	See table 1
Outcomes	Clinical respiratory illness (CRI), influenza-like illness (ILI) and laboratory confirmed respiratory virus infection. (1) Clinical respiratory illness (CRI), defined as two or more respiratory symptoms or one respiratory symptom and a systemic symptom; (2) influenza-like illness (ILI), defined as fever $\geq 38^\circ\text{C}$ plus one respiratory symptom and (3) laboratory-confirmed viral respiratory infection. Laboratory confirmation was by nucleic acid detection using multiplex reverse transcriptase PCR (RT-PCR) for 17 respiratory viruses. Adverse events associated with mask use
Notes	Government funded
MacIntyre 2011	
Method	A cluster randomized clinical trial (RCT) of 1441 HCWs in 15 Beijing hospitals was performed during the 2008/2009 winter. Participants wore masks or respirators during the entire work shift for 4 weeks. Outcomes included clinical respiratory illness (CRI), influenza-like illness (ILI), laboratory confirmed respiratory virus infection and influenza. A convenience no-mask/respirator group of 481 health workers from nine hospitals was compared.
Participants	Participants were hospital HCWs aged ≥ 18 years from the emergency departments and respiratory wards of 15 hospitals. These wards were selected as high-risk settings in which repeated and multiple exposures to respiratory infections are expected.
Interventions	See table 1
Outcomes	Clinical respiratory illness (CRI) Influenza-Like-Illness laboratory-confirmed viral respiratory infection laboratory-confirmed influenza A or B (i) Clinical respiratory illness (CRI), defined as two or more respiratory or one respiratory symptom and a systemic symptom; (ii)

	ILI, defined as fever $\geq 38^{\circ}\text{C}$ plus one respiratory symptom (i.e. cough, runny nose, etc.); (iii) laboratory-confirmed viral respiratory infection (detection of adenoviruses, human metapneumovirus, coronavirus 229E/NL63, parainfluenza viruses 1, 2 and 3, influenza viruses A and B, respiratory syncytial virus A and B, rhinovirus A/B and coronavirus OC43/HKU1 by multiplex PCR); (iv) laboratory-confirmed influenza A or B and (v) adherence with mask/respirator use. Reported problems associated with using the masks or respirators
Notes	Funding source unknown; control arm not randomised so is ignored
MacIntyre 2013	
Method	A cluster randomized trial
Participants	A total of 1,669 nurses and doctors for 68 emergency departments and respiratory wards of 19 Beijing hospitals were included. Inclusion criteria: any nurse or doctor aged 18 years or older who worked full-time in the emergency or respiratory wards was eligible. Exclusion: health care workers if they (1) were unable or refused to consent; (2) had beards, long moustaches, or long facial hair stubble; (3) had a current respiratory illness, rhinitis, and/or allergy; or (4) worked part-time or did not work in the aforementioned wards or departments.
Interventions	See table 1
Outcomes	Laboratory: 1) laboratory-confirmed viral respiratory infection in symptomatic subjects, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (Seegen, Inc., Seoul, Korea). 2) Laboratory-confirmed influenza A or B in symptomatic subjects. 3) Laboratory-confirmed bacterial colonization in symptomatic subjects, defined as detection of <i>Streptococcus pneumoniae</i> , <i>legionella</i> , <i>Bordetella pertussis</i> , <i>chlamydia</i> , <i>Mycoplasma pneumoniae</i> , or <i>Hemophilus influenzae</i> type B by multiplex polymerase chain reaction (Seegen, Inc.). Effectiveness: Clinical respiratory illness (CRI) defined as two or more respiratory symptoms or one respiratory symptom and a systemic symptom. ILI, defined as fever (38°C) plus one respiratory symptom Safety: Adverse effects measured using a semistructured questionnaire. Investigators stated that there was higher reported adverse effects and discomfort of N95 respirators compared with the other two arms, In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm ($P, 0.001$).
Notes	Compliance with the product was the highest in the targeted N95 arm (82%; 422 of 516), then the medical mask arm (66%; 380 of 572), and the N95 arm (57%; 333 of 581) and these differences were statistically significant ($P, 0.001$). The period study conducted: December 28, 2009 to February 7, 2010 Funding: Unclear
MacIntyre 2016	
Method	Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness in 6 major hospitals in 2 districts of Beijing, China. Index cases with ILI were randomly allocated to medical mask ($n=123$) and control arms ($n=122$). Since 43 index cases in the control arm also used a mask during the study period, an as-treated post hoc analysis was performed by comparing outcomes among household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no-mask group).
Participants	245 index cases with ILI.

Interventions	See table 1
Outcomes	<p>Clinical respiratory illness, ILI and laboratory-confirmed viral respiratory infection.</p> <p>(1) clinical respiratory illness (CRI), defined as two or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat or sneezes) or one respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches); (2) ILI, defined as fever $\geq 38^{\circ}\text{C}$ plus one respiratory symptom; and (3) laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenza viruses 1, 2 and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing (NAT) using a commercial multiplex PCR</p> <p>No safety outcomes reported</p>
Notes	Government funded
Radonovich 2019	
Method	cluster-randomized, multicenter, pragmatic effectiveness trial
Participants	<p>Healthcare workers in outpatient settings serving adult and pediatric patients with a high prevalence of acute respiratory illness.</p> <p>Inclusion criteria: participants were aged at least 18 years employed at one of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥ 24 hours weekly) and worked primarily at the study site (defined as $\geq 75\%$ of working hours). Exclusion criteria were medical conditions precluding safe participation or anatomic features that could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.</p> <p>All participants in a cluster worked in the same outpatient clinic or outpatient setting. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation</p>
Interventions	See table 1
Outcomes	<p>Laboratory. Primary_outcome: The incidence of laboratory-confirmed influenza, defined as:</p> <ul style="list-style-type: none"> • Detection of influenza A or B virus by reverse-transcription polymerase chain reaction in an upper respiratory specimen collected within 7 days of symptom onset. • Detection of influenza from a randomly obtained swab from an asymptomatic participant. • Influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in hemagglutination inhibition antibody titers to influenza A or B virus between pre-season and post-season serological samples deemed not attributable to vaccination. <p>Effectiveness. Secondary_outcomes: The incidence of 4 measures of viral respiratory illness or infection as follows:</p> <ol style="list-style-type: none"> 1. Acute respiratory illness with or without laboratory confirmation. 2. Laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by polymerase chain reaction or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis. 3. Laboratory confirmed respiratory illness, identified as previously described, (defined as self-reported acute respiratory illness plus the presence of at least polymerase chain reaction- confirmed viral pathogen in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from pre-intervention to post-intervention serum antibody titers to influenza A or B virus;

	<p>4. Influenza-like illness, defined as temperature of at least 100°F (37.8°C) plus cough and/or a sore throat, with or without laboratory confirmation</p> <p>Safety: No serious study-related adverse events were reported. Nineteen participants reported skin irritation or worsening acne during years 3 and 4 at one site in the N95 respirator group.</p>
Notes	<p>The Period study conducted: September 2011 and May 2015, with final follow-up on June 28, 2016</p> <p>Funding: Government</p> <p>Compliance: Adherence was reported on daily surveys 22□330 times in the N95 respirator group and 23□315 times in the medical mask group. “Always” was reported 14□566 (65.2%) times in the N95 respirator group and 15□186 (65.1%) times in the medical mask group; “sometimes,” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never,” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall,” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group ($P=.$84) because of lack of response to surveys or lack of adherence opportunities (ie, participants did not encounter an individual with respiratory signs or symptoms). Analyzed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group</p>

Appendix

Appendix 1: Search strings for databases

PubMed search run 09/03/2020

("Influenza, Human"[Mesh] OR "Influenzavirus A"[Mesh] OR "Influenzavirus B"[Mesh] OR "Influenzavirus C"[Mesh] OR Influenza[tiab] OR "Respiratory Tract Diseases"[Mesh] OR "Bacterial Infections/transmission"[Mesh] OR Influenzas[tiab] OR "Influenza-like"[tiab] OR ILI[tiab] OR Flu[tiab] OR Flus[tiab] OR "Common Cold"[Mesh:NoExp] OR "common cold"[tiab] OR colds[tiab] OR coryza[tiab] OR coronavirus[Mesh] OR "sars virus"[Mesh] OR coronavirus[tiab] OR Coronaviruses[tiab] OR "coronavirus infections"[Mesh] OR "severe acute respiratory syndrome"[Mesh] OR "severe acute respiratory syndrome"[tiab] OR "severe acute respiratory syndromes"[tiab] OR sars[tiab] OR "respiratory syncytial viruses"[Mesh] OR "respiratory syncytial virus, human"[Mesh] OR "Respiratory Syncytial Virus Infections"[Mesh] OR "respiratory syncytial virus"[tiab] OR "respiratory syncytial viruses"[tiab] OR rsv[tiab] OR parainfluenza[tiab] OR ((Transmission[tiab]) AND (Coughing[tiab] OR Sneezing[tiab])) OR ((respiratory[tiab] AND Tract[tiab]) AND (infection[tiab] OR Infections[tiab] OR illness[tiab])))

AND

("Hand Hygiene"[Mesh] OR handwashing[tiab] OR hand-washing[tiab] OR ((Hand[tiab] OR Alcohol[tiab]) AND (wash[tiab] OR Washing[tiab] OR Cleansing[tiab] OR Rinses[tiab] OR hygiene[tiab] OR rub[tiab] OR Rubbing[tiab] OR sanitiser[tiab] OR sanitizer[tiab] OR cleanser[tiab] OR disinfected[tiab] OR Disinfectant[tiab] OR Disinfect[tiab] OR antiseptic[tiab] OR virucid[tiab])) OR "gloves, protective"[Mesh] OR Glove[tiab] OR Gloves[tiab] OR Masks[Mesh] OR "respiratory protective devices"[Mesh] OR facemask[tiab] OR Facemasks[tiab] OR mask[tiab] OR Masks[tiab] OR respirator[tiab] OR respirators[tiab] OR "Protective Clothing"[Mesh:NoExp] OR "Protective Devices"[Mesh] OR "patient isolation"[tiab] OR ((school[tiab] OR Schools[tiab]) AND (Closure[tiab] OR Closures[tiab] OR Closed[tiab]))) OR Quarantine[Mesh] OR quarantine[tiab] OR "Hygiene intervention"[tiab] OR "Mouthwashes"[Mesh] OR gargling[tiab] OR "nasal tissues"[tiab])

AND

("Communicable Disease Control"[Mesh] OR "Disease Outbreaks"[Mesh] OR "Disease Transmission, Infectious"[Mesh] OR "Infection Control"[Mesh] OR Transmission[sh] OR "Prevention and control"[sh] OR "Communicable Disease Control"[tiab] OR "Secondary transmission"[tiab] OR ((Reduced[tiab] OR Reduce[tiab] OR Reduction[tiab] OR Reducing[tiab] OR Lower[tiab])) AND (Incidence[tiab] OR Occurrence[tiab] OR Transmission[tiab] OR Secondary[tiab])))

AND

(Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])

NOT

(Animals[Mesh] not (Animals[Mesh] and Humans[Mesh])))

NOT

("Case Reports"[pt] OR Editorial[pt] OR Letter[pt] OR Meta-Analysis[pt] OR "Observational Study"[pt] OR "Systematic Review"[pt] OR "Case Report"[ti] OR "Case series"[ti] OR Meta-Analysis[ti] OR "Meta Analysis"[ti] OR "Systematic Review"[ti])

Cochrane CENTRAL run 09/03/2020

([mh "Influenza, Human"] OR [mh "Influenzavirus A"] OR [mh "Influenzavirus B"] OR [mh "Influenzavirus C"] OR Influenza:ti,ab OR [mh "Respiratory Tract Diseases"] OR Influenzas:ti,ab OR "Influenza-like":ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR [mh ^"Common Cold"] OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR [mh coronavirus] OR [mh "sars virus"] OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR [mh "coronavirus infections"] OR [mh "severe acute respiratory syndrome"] OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR [mh "respiratory syncytial viruses"] OR [mh "respiratory syncytial virus, human"] OR [mh "Respiratory Syncytial Virus Infections"] OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR parainfluenza:ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))

AND

([mh "Hand Hygiene"] OR handwashing:ti,ab OR "hand-washing":ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitiser:ti,ab OR sanitizer:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR [mh "gloves, protective"] OR Glove:ti,ab OR Gloves:ti,ab OR [mh Masks] OR [mh "respiratory protective devices"] OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR [mh ^"Protective Clothing"] OR [mh "Protective Devices"] OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR [mh Quarantine] OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR [mh Mouthwashes] OR gargling:ti,ab OR "nasal tissues":ti,ab)

AND

([mh "Communicable Disease Control"] OR [mh "Disease Outbreaks"] OR [mh "Disease Transmission, Infectious"] OR [mh "Infection Control"] OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab)))

Embase run 09/03/2020

('influenza'/exp OR Influenza:ti,ab OR 'Respiratory Tract Disease'/exp OR Influenzas:ti,ab OR Influenza-like:ti,ab OR ILI:ti,ab OR Flu:ti,ab OR Flus:ti,ab OR 'Common Cold'/de OR "common cold":ti,ab OR colds:ti,ab OR coryza:ti,ab OR 'coronavirus'/exp OR 'SARS coronavirus'/exp OR coronavirus:ti,ab OR Coronaviruses:ti,ab OR 'coronavirus infection'/exp OR 'severe acute respiratory syndrome'/exp OR "severe acute respiratory syndrome":ti,ab OR "severe acute respiratory syndromes":ti,ab OR sars:ti,ab OR 'Pneumovirus'/exp OR 'Human respiratory syncytial virus'/exp OR "respiratory syncytial virus":ti,ab OR "respiratory syncytial viruses":ti,ab OR rsv:ti,ab OR

parainfluenza:ti,ab OR ((Transmission) AND (Coughing OR Sneezing)) OR ((respiratory:ti,ab AND Tract) AND (infection:ti,ab OR Infections:ti,ab OR illness:ti,ab)))

AND

('hand washing'/exp OR handwashing:ti,ab OR hand-washing:ti,ab OR ((Hand:ti,ab OR Alcohol:ti,ab) AND (wash:ti,ab OR Washing:ti,ab OR Cleansing:ti,ab OR Rinses:ti,ab OR hygiene:ti,ab OR rub:ti,ab OR Rubbing:ti,ab OR sanitiser:ti,ab OR sanitizer:ti,ab OR cleanser:ti,ab OR disinfected:ti,ab OR Disinfectant:ti,ab OR Disinfect:ti,ab OR antiseptic:ti,ab OR virucid:ti,ab)) OR 'protective glove'/exp OR Glove:ti,ab OR Gloves:ti,ab OR 'mask'/exp OR 'gas mask'/exp OR facemask:ti,ab OR Facemasks:ti,ab OR mask:ti,ab OR Masks:ti,ab OR respirator:ti,ab OR respirators:ti,ab OR 'protective clothing'/de OR 'protective equipment'/exp OR "patient isolation":ti,ab OR ((school:ti,ab OR Schools:ti,ab) AND (Closure:ti,ab OR Closures:ti,ab OR Closed:ti,ab)) OR 'Quarantine'/exp OR quarantine:ti,ab OR "Hygiene intervention":ti,ab OR 'mouthwash'/exp OR gargling:ti,ab OR "nasal tissues":ti,ab)

AND

('Communicable Disease Control'/exp OR 'epidemic'/exp OR 'disease transmission'/exp OR 'Infection Control'/exp OR "Communicable Disease Control":ti,ab OR "Secondary transmission":ti,ab OR ((Reduced:ti,ab OR Reduce:ti,ab OR Reduction:ti,ab OR Reducing:ti,ab OR Lower:ti,ab) AND (Incidence:ti,ab OR Occurrence:ti,ab OR Transmission:ti,ab OR Secondary:ti,ab)))

AND

(random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

CINAHL run 09/03/2020

((MH "Influenza, Human+") OR (MH "Orthomyxoviridae+") OR TI Influenza OR AB Influenza OR (MH "Respiratory Tract Diseases+") OR TI Influenzas OR AB Influenzas OR TI Influenza-like OR AB Influenza-like OR TI ILI OR AB ILI OR TI Flu OR AB Flu OR TI Flus OR AB Flus OR (MH "Common Cold+") OR TI "common cold" OR AB "common cold" OR TI colds OR AB colds OR TI coryza OR AB coryza OR (MH "coronavirus+") OR (MH "sars virus+") OR TI coronavirus OR AB coronavirus OR TI Coronaviruses OR AB Coronaviruses OR (MH "coronavirus infections+") OR (MH "severe acute respiratory syndrome+") OR TI "severe acute respiratory syndrome" OR AB "severe acute respiratory syndrome" OR TI "severe acute respiratory syndromes" OR AB "severe acute respiratory syndromes" OR TI sars OR AB sars OR (MH "respiratory syncytial viruses+") OR TI "respiratory syncytial virus" OR AB "respiratory syncytial virus" OR TI "respiratory syncytial viruses" OR AB "respiratory syncytial viruses" OR TI rsv OR AB rsv OR TI parainfluenza OR AB parainfluenza OR ((Transmission) AND (Coughing OR Sneezing)) OR ((TI respiratory OR AB respiratory AND Tract) AND (TI infection OR AB infection OR TI Infections OR AB Infections OR TI illness OR AB illness)))

AND

((MH "Handwashing+") OR TI handwashing OR AB handwashing OR TI hand-washing OR AB hand-washing OR ((TI Hand OR AB Hand OR TI Alcohol OR AB Alcohol) AND (TI wash OR AB wash OR TI Washing OR AB Washing OR TI Cleansing OR AB Cleansing OR TI Rinses OR AB Rinses OR TI hygiene OR AB hygiene OR TI rub OR AB rub OR TI Rubbing OR AB Rubbing OR TI sanitiser OR AB sanitiser OR

TI sanitizer OR AB sanitizer OR TI cleanser OR AB cleanser OR TI disinfected OR AB disinfected OR TI Disinfectant OR AB Disinfectant OR TI Disinfect OR AB Disinfect OR TI antiseptic OR AB antiseptic OR TI virucid OR AB virucid)) OR (MH "gloves+") OR TI Glove OR AB Glove OR Gloves OR (MH "Masks+") OR (MH "respiratory protective devices+") OR TI facemask OR AB facemask OR TI Facemasks OR AB Facemasks OR TI mask OR AB mask OR TI Masks OR AB Masks OR TI respirator OR AB respirator OR TI respirators OR AB respirators OR (MH "Protective Clothing") OR (MH "Protective Devices+") OR TI "patient isolation" OR AB "patient isolation" OR ((TI school OR AB school OR TI Schools OR AB Schools) AND (TI Closure OR AB Closure OR TI Closures OR AB Closures OR TI Closed OR AB Closed)) OR (MH "Quarantine+") OR TI quarantine OR AB quarantine OR TI "Hygiene intervention" OR AB "Hygiene intervention" OR (MH "Mouthwashes+") OR TI gargling OR AB gargling OR TI "nasal tissues" OR AB "nasal tissues")

AND

((MH "Infection Control") OR (MH "Disease Outbreaks") OR (MH "Infection Control") OR TI "Communicable Disease Control" OR AB "Communicable Disease Control" OR TI "Secondary transmission" OR AB "Secondary transmission" OR ((TI Reduced OR AB Reduced OR TI Reduce OR AB Reduce OR TI Reduction OR AB Reduction OR TI Reducing OR AB Reducing OR TI Lower OR AB Lower) AND (TI Incidence OR AB Incidence OR TI Occurrence OR AB Occurrence OR TI Transmission OR AB Transmission OR TI Secondary OR AB Secondary)))

AND

((MH "Clinical Trials") OR (MH "Quantitative Studies") OR TI placebo* OR AB placebo* OR (MH "Placebos") OR (MH "Random Assignment") OR TI random* OR AB random* OR TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR TI clinic* trial* OR AB clinic* trial* OR PT clinical trial)